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RECORD OF ORAL HEARING

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MARIA ADELE PACCIARINI, OLGA VALOTA,
and DAVID KERR

Appeal 2008-5301
Application 09/786,998
Technology Center 1600

Oral Hearing Held: February 3, 2009

Before DONALD E. ADAMS, LORA M. GREEN, and
MELANIE L. McCOLLUM, *Administrative Patent Judges.*

ON BEHALF OF THE APPELLANTS:

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P R O C E E D I N G S

MS. BOBO-ALLEN: Calendar No. 8, Appeal No. 5301. Mr. Bernstein.

JUDGE ADAMS: Thank you. Good morning, Mr. Bernstein.

MR. BERNSTEIN: Good morning, Judge Adams.

JUDGE ADAMS: We're familiar with your record. You'll have 20 minutes. You can begin when you're ready and as long as you do me the favor of spelling your name into the record for us.

MR. BERNSTEIN: I'd be happy to do that. Bernstein, B E R N S T E I N, Peter, from Scully, Scott, Murphy, and Presser representing the appellant.

May it please the Board, as I just mentioned, I'm Peter Bernstein from Scully, Scott. I wanted to make sure I reserved 5 minutes for rebuttal out of my 20 minutes, if that's possible.

JUDGE ADAMS: Usually that's a reservation we make when the examiner is presenting arguments.

MR. BERNSTEIN: Okay, so if the examiner is --

JUDGE ADAMS: If you wouldn't mind, if we have questions, we'll just ask you along the way and that will be fine.

MR. BERNSTEIN: Not a problem. Just to underscore the issue here, this application is about the unexpected efficacy of intra-hepatic administration of methoxy-morpholino-doxorubicin, or MMDX, and we'll refer to it as MMDX throughout this hearing, and also, the therapeutic agent that's administered with it in conjunction. All the claims currently are rejected based on 103 based on the combination of four references. I assume the panel is familiar with the references. But I think before we get to the references, what's really critical about the appellant's position is that there's a fundamental structural difference that the examiner has steadfastly refused to

acknowledge. His position is premised on this alleged structural relatedness between MMDX and doxorubicin. In fact, and as is borne out in the record, the methoxy-morpholino group is the significantly larger, bulky group that's attached to the sugar moiety on the molecule. And the difference between doxorubicin and MMDX is so fundamental because the amino group, which doxorubicin has, ends up conferring different biological activities and that's exemplified and is brought out in the specification. You're talking about an unexpected efficacy of an 80 times more effective agent when you're using MMDX compared to doxorubicin.

So, you have a fundamental structural difference that leads, leads to a functional difference that's replete throughout the record. These, these are illustrated in an amendment from February of 2005 demonstrating that structural alterations profoundly affect the interaction with biological targets so influencing the mechanism of action and eventually the activity of these drugs. And that's in Capranico which is in the February 2005 amendment and there are other references as well in the record. So --

JUDGE McCOLLUM: Is Capranico discussed in the -- on the record of -- the record on appeal?

MR. BERNSTEIN: I believe it's subsumed within the, within the arguments, but maybe not specifically called out in, in the brief.

JUDGE McCOLLUM: Okay.

MR. BERNSTEIN: It, it's -- I'm referring to it from the February 2005 amendment. So, so, even, even without specific reference to Capranico, the, the structural difference drives the whole analysis. If, if we get past the structural difference and a recognition that that is what's critical

here -- because in oncology you can't just say that because it's a member of a class of anthracyclines that it's going to have the same effect. In fact, MMDX does not have the same effect, it's 80 times more potent. And when it's administered with the therapeutic agent, the, the lipiodol, you end up having it stay in the tumor for an extended period of time evidencing further efficacy. So, I think that's critical for the panel to understand in connection with their analysis of this case.

The, the four references I referred to, one, Bargiotti, was raised most recently in the record by the Examiner. And at Bargiotti -- there are many deficiencies with each of the references, and I can -- I'll go through them briefly. But it's obviously the combination of the references that the Examiner has, has cobbled together here, I think with a significant amount of hindsight, by the way, but I'm sure you've heard that many times before. But the bottom line is the principal reference, Bargiotti, teaches -- does not teach, does not suggest intra-hepatic administration of MMDX. It does not teach or suggest agents that increase MMDX's time selectively in the liver. There's no teaching or suggestion, in fact, of treating liver tumors in Bargiotti. So, Bargiotti is really a very weak primary reference.

The Kuhl reference is brought in secondarily --

JUDGE GREEN: Just to get back to Bargiotti just for a second.

MR. BERNSTEIN: Sure, go ahead, yes.

JUDGE GREEN: Column 11, it does state that the -- that some of these compounds are much more cytotoxic than the parent drug, right?

MR. BERNSTEIN: If you could refer me to exactly what you're referring to because I don't want to --

JUDGE GREEN: I'm not sure what this, what -- how these relate to the, the MMDX, but about line 48 --

MR. BERNSTEIN: Yes, yes.

JUDGE GREEN: -- it says the new anthracyclines result is more cytotoxic than the parent drug on doxorubicin-resistant cell lines and are active in vivo against the same resistant cell lines.

MR. BERNSTEIN: Yes, and I think what we're talking about here is a completely different tumor. We're talking about a mammary tumor and not a liver tumor. So, I think that's an important distinction to bear in mind.

JUDGE GREEN: But it's still a solid tumor, right?

MR. BERNSTEIN: It's not -- I would say it's not 100 percent clear from the reference, but it refers to a mammary human carcinoma, MX-1.

JUDGE GREEN: It says studied in solid tumors such as mammary -- in human carcinoma, MX-1.

MR. BERNSTEIN: Right, so, so most likely it is a solid tumor, but I would submit and, and the appellants submit that you cannot extrapolate from one tumor to the next necessarily. We're talking about liver cancer compared to a mammary cancer and a cell line.

So, going back to Kuhl, the secondary reference, here that's really an in vitro study of MMDX on blood tumors, on liquid tumors. Here we have a clear distinction from the solid tumors as well. You, you don't have any teaching or suggestion in Kuhl that -- of an agent that selectively stays in the liver. There's no treatment of liver tumors, only some potency data, and clearly no, no teaching or suggestion of intra-hepatic delivery as well.

JUDGE GREEN: But Kuhl does teach that it is -- has a broad spectrum of anti-tumor activity, this is just in the abstract, and that it is activated in the liver to be 10 times more potent which could be motivation why you'd want to keep it in the liver for a little longer no matter what tumor you were, you were treating. I mean for the composition claims because the composition claims are not limited to treating liver cancer, right?

MR. BERNSTEIN: Correct. It's just, it's simply MMDX -- well, the principal claim, the main claim, is just MMDX and the agent that stays selectively in the liver.

JUDGE GREEN: Right, and here Kuhl teaches that it's activated in the liver.

MR. BERNSTEIN: I think Kuhl does not get you any reasonable expectation of success that the composition would work for treating, number one, and number two, Kuhl --

JUDGE GREEN: But he teaches there's a broad spectrum of pre-clinical anti-tumor activity.

MR. BERNSTEIN: But not, not in terms with -- not in combination with an agent that makes it stay selectively in the liver.

JUDGE GREEN: But you have a motivation to keep it in the liver so that it becomes more activated.

MR. BERNSTEIN: I don't --

JUDGE GREEN: I mean it does say that it's activated in the liver to be a 10 times more potent metabolite.

MR. BERNSTEIN: But I think the teaching -- I think you might be referring to the abstract. I'm not sure exactly where you're reading from, but Kuhl --

JUDGE GREEN: I'm looking at the abstract.

MR. BERNSTEIN: Okay. Kuhl, Kuhl is all about lymphoma and leukemia. It's about blood tumors, not solid tumors.

JUDGE GREEN: I understand that, but your composition claim is not towards any specific type. It's just the MMDX and an agent which will remain selectively in the liver, in the liver tumor. I mean --

MR. BERNSTEIN: I agree that's what the claim is. I, I see your -- I understand your point. I, I think the critical distinction again is with respect to the composition claims. If we just want to focus on the composition claims is that the agent that stays selectively in the liver, which is described in detail in the specification, is nowhere toward a suggestion in Kuhl. We can, we can agree to disagree for now, but focusing on the method claims and the method treatment claims and the methods of ensuring less systematic exposure of MMDX with, with the description in the application, you, you go to the Nakamura reference which now we're back at doxorubicin again. And, again, going back to my original point, which I'm not going to belabor, the fundamental structural difference is -- this, this -- Nakamura, if anything, is a complete teaching away because you have MMDX with doxorubicin. But a close reading of Nakamura is really focused -- it's really focused on the LPD, or the selective agent, its use and, and its manifestation in, in the body. It's not a therapeutic -- there's one case that's described. It's not 100

percent clear what the tumor is, but it appears to be a liver tumor, but, again, we're giving doxorubicin and an agent, not MMDX.

JUDGE GREEN: But I mean there's no teaching away. I mean you said this is a teaching away? There's nothing in Nakamura, at least in the abstract that's before us, that suggests you wouldn't use MMDX with LPD. And obviously, this does teach liver cancer specifically, and it teaches the combination of two agents. Obviously, I totally agree that what they're calling ADM here is not MMDX, but the question becomes is it obvious based on the, the two -- the B reference and the K reference to substitute MMDX for ADM?

MR. BERNSTEIN: Definitely not, definitely not, because, again, there's not -- we agree MMDX is not at all taught or suggested in Nakamura. And we have a full translation of the full reference, I think that's been submitted on the record as well. You might be just looking at the abstract. But in any case, I'll represent to you that there's absolutely no teaching or suggestion of MMDX at all.

There, there is a combination of agents, but it sounds like you're making kind of an obvious to-try argument. And I would respond to you by saying, well, even if that's the case, there would be -- there's no predictability that this would be successful because you have, you have no indication of, of the recognition that the present invention has of an 80 times more effective or more potent combination. You, you can't make the leap, you can't make the substitution here because it's simply just not taught or suggested. And, again, even if you argued obvious-to-try, I think the stronger argument is no expectation of success.

JUDGE McCOLLUM: Well, there's no expectation of success or no expectation of gaining 80 percent more?

MR. BERNSTEIN: There's no expectation that it would even be a successful treatment from, from there, and certainly no expectation that you'd have any more potency.

JUDGE McCOLLUM: I mean because -- I mean, for example, the Kuhl reference just says it's a -- I mean both of these references describe them, describe them as anti-tumor, they call it broad spectrum. I mean it seems like that would be at least a reasonable expectation that maybe that it would treat tumors. So, to say that there's no reasonable expectation of success, now the 80-fold increase is more an unexpected result type of thing.

MR. BERNSTEIN: Absolutely.

JUDGE McCOLLUM: And I'm trying to distinguish whether there's a prima facie case, and then we can discuss whether there's unexpected results, but you're saying there's not even a prima facie.

MR. BERNSTEIN: Well, not -- I think this is rebutted by -- certainly by the unexpected success, the unexpected results, and --

JUDGE McCOLLUM: So, is there an -- where is the -- can you point me to the -- I mean I know you -- in the spec it talks about an 80 percent -- 80-fold -- I think in the spec it said that?

MR. BERNSTEIN: That's correct, page 2 --

JUDGE McCOLLUM: It mentioned that?

MR. BERNSTEIN: -- that's correct.

JUDGE McCOLLUM: No --

JUDGE GREEN: But that's just for the compounds themselves, that's not to your composition.

MR. BERNSTEIN: Oh, I think it's to the composition.

JUDGE McCOLLUM: Well, let me see, I mean --

JUDGE GREEN: If you look -- look at page 2 of the specification, the second full paragraph, and show me where that is pointing to the composition, your claimed composition.

JUDGE McCOLLUM: In fact, that's administered by IV.

MR. BERNSTEIN: The, the administered -- yeah, the IV dose was interpreted to mean composition. I see your point, it says compound. I thought it said composition and I'm sorry, it says compound.

JUDGE GREEN: So, it's just the difference between MMDX and --

MR. BERNSTEIN: And doxorubicin, yes.

JUDGE GREEN: Which is -- okay.

MR. BERNSTEIN: Which is -- good point. Yeah, I, I really thought it said composition, it says compound.

JUDGE McCOLLUM: And, and I have -- you know this -- almost -- I wasn't even clear in the spec whether this was background of -- or whether this was -- so, I mean there's definitely nothing -- to me reading this, I wasn't clear that this was some unexpected thing. It almost read like this might be the background that we -- that it's known in the art that it has this increased -- 80-fold increase. So, I'm not -- there's no -- so I didn't see any evidence that this was something that's unexpected.

MR. BERNSTEIN: Okay, I, I think that is unexpected and not, not background at all, number one. Number two, we can't take credit for having

written the case because it was written by another firm in an era a long time ago. So, I, I appreciate the structure of the application. It's not the way we would do it, but that is the unexpected result in, in the context of MMDX versus doxorubicin.

JUDGE GREEN: But we do have the Bargiotti reference teaching that it's more potent --

JUDGE McCOLLUM: As does the Kuhl reference.

JUDGE GREEN: -- as does the Kuhl reference. So, how -- we -- I, I guess I'm not seeing how this supports any unexpected results. You don't have -- I mean you don't have any data showing that you're the ones that discovered this is 80-fold more -- and not only that, you're not limited to this particular embodiment of introducing an IV. I mean your embodiment's completely different because you want to put it straight into the, the liver with this extra compound in your composition.

MR. BERNSTEIN: Right. So, again, Kuhl -- and, and it's really a potency, a potency reference dealing with application in vitro to a different kind of tumor. So, I think its applicability is very limited.

JUDGE McCOLLUM: Unless there's unexpected results. It says it's highly, it's highly potent when administered, so this, this part on page 2 is also about potency, is it not or am I reading that incorrectly?

MR. BERNSTEIN: No, I think, I think -- but the difference here is you're dealing with in the specification an in vivo tumor application. I think Kuhl is dealing with a cell line, a lymphoma, a liquid cell, a different kind of tumor. So, I think they're distinguished on that basis. It, it's really apples and oranges I think when you come to Kuhl because, again, the in vitro

potency assay in lymphoma and leukemia is different from an in vivo application to a liver tumor. And I, I wanted to get back to your point about Bargiotti. You, you mentioned, again, potency. I, I think Bargiotti is -- is that what your point was?

JUDGE GREEN: Well, the part where you discussed before where on column 14 --

MR. BERNSTEIN: Column 11, column 14, okay.

JUDGE GREEN: Column, column 11, I'm sorry.

MR. BERNSTEIN: That's okay.

JUDGE GREEN: That they're more cytotoxic than the parent drug.

MR. BERNSTEIN: Right, they're, they're giving -- according to Table 6, and I'm looking at -- on column 12 which I think relates to the, the evidence you're pointing to. They talk about administration every seven days -- three times every seven days at milligram per kilogram quantities. I think the applications of the dependent claim is talking about microgram quantities of MMDX, not milligram if I'm not mistaken. But, again, Bargiotti is another apples and oranges type comparison. Bargiotti is, at best, a mammary tumor. You know, the population that's obviously suffering mammary tumors is more likely to be women. And statistically and as described in the application, liver tumors are predominately or most likely to be found in men at least 4:1 according to the application. So, I don't think you can extrapolate mammary tumor right to liver tumor. I, I don't think you can do that. And on a primary basis -- and even on a, a metastatic basis, if you were to try to make that extrapolation, I think it would be completely unexpected. You wouldn't want to even give these

agents because at that point usually a metastasis to the liver from a breast tumor is not likely to have a positive outcome in a period of months. So, there's really no likelihood that you'd even administer an MMDX in that -- or doxorubicin, or anything for that matter, because they're not likely to be effective. So, I think, I think we're dealing with solid tumors which is what Bargiotti talks about. You can't go from mammary to, to liver.

JUDGE ADAMS: Okay, you're out of time. We can extend that a little bit more if you just want to wrap things up.

MR. BERNSTEIN: Okay, thank you. I actually -- the only other point I would make, if I could, is going back to the Kuhl reference, it teaches that MMDX is activated with liver to a highly active metabolite, and I think you pointed that out. And the application talks about MMDX is transformed into highly cytotoxic metabolites. So, with respect to Gorbunova which we really didn't talk, talk about as the fourth reference, it's really in our minds cumulative with Nakamura, one, one of the tertiary references. The examiner is admitting that Gorbunova teaches intra-arterial infusion. Chemotherapy allows for the creation of very high concentrations of anti-tumor agents. Therefore, in view of the teachings from the prior art that very high concentrations of anti-tumor agents would be created by intra-hepatic administration and MMDX, it's -- and that MMDX is transformed into a highly cytotoxic metabolite, one skilled in the art would not have been motivated to even attempt to try to use MMDX in intra-hepatic administration or for the treatment of liver, liver tumors because it would be expected to cause very significant toxicity. That was the only other point I wanted to make.

JUDGE ADAMS: Do you have any questions?

JUDGE GREEN: No.

JUDGE McCOLLUM: No.

JUDGE ADAMS: Thank you very much for your time.

MR. BERNSTEIN: Thank you all very much.

(Whereupon, the hearing concluded at 11:03 a.m., on February 3, 2009.)